Applicants respectfully submit that the Examiner's rejection is legally improper for the reasons of record.

In any event, from the results described at page 30 of the present specification, it is clear that using the present invention, an engraftment rate of 100% is achieved.

More specifically, at page 30, lines 5-7 of the present application, it is taught that "an engraftment rate of 100% for the donor (CDF1)'s skin graft at week 23 (on the 167th day) after transplantation".

As described on page 1, lines 6-7, and page 5, lines 14-16, etc., of the present specification, "immunological tolerance" is indispensable to maintenance of transplanted organs. The "immunological tolerance" meant by the present invention is the condition where no immunological reaction occurs against the transplanted organs, i.e., the condition free from graft rejection. If the immunological tolerance according to the present invention is achieved, as a matter of course, a 100% engraftment rate can be attained.

Hence, in view of the amendment to Claim 9 to include after step (b), an additional step (c) involving transplanting the organ, whereby an engraftment rate of 100% is achieved, it is believed that the Examiner's rejection has been rendered moot.

Accordingly, Applicants respectfully submit that the claims clearly and definitely recite the invention of interest, and thus request withdrawal of the Examiner's rejection.

In paragraph 8, on page 3 of the Office Action, the Examiner maintains the rejection of Claims 9-10 and 12 under 35 U.S.C. § 103 as being unpatentable over Ildstadt in view of Zhang et al.

Specifically, the Examiner notes Applicants' arguments that Ildstadt does not teach the administration of whole blood. However, it is the Examiner's position that the discussion noted by Applicants in Ildstadt is of approaches used in the art that have resulted in mixed chimerism, and are not an indication that T cell depleted marrow was used by Ildstadt therein.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

As the Examiner acknowledges, an important factor that differentiates the present invention from Ildstad is that, in the present invention, WBMCs (whole blood marrow cells) are administered by PV (portal venous administration), and organ transplantation is performed within the same day of PV (one-day protocol).

Claim 9 has been amended to clarify the above-described differences. Specifically, by following the steps according to amended Claim 9, i.e.,

(a) conducting TBI (total body irradiation) using a radiation dose of at least 6.5 Gy,

(b) administering WBMC's by PV, and

(c) transplanting the organ within the same day (see Test Example 4 and Figure 2 as the WBMC's are administered (a <u>one-day</u> protocol),

a 100% engraftment rate for the organ transplanted can be achieved.

Support for the amendment regarding the one-day protocol can be found in cancelled Claim 12.

The one-day protocol of organ transplantation is highly advantageous since it enables organ transplantation from brain

dead donors, whose brain function has totally ceased for 24 hours.

In contrast, organ transplantation from such donors can not be carried out by the method of Ildstad, wherein the organ transplantation is performed 1-7 months after the bone marrow call administration (see column 21, lines 60-67 in the section of "6.2.9. Evidence for Specific Tolerance *In Vivo* to Donor-Type Skin Grafts" in Ildstad).

As described above, Ildstad merely teaches skin graft conducted 1-7 months after the bone marrow cell administration. Therefore, the teachings of Ildstad would not lead a person skilled in the art to arrive at a technique by which an engraftment rate of 100% can be achieved when organ transplantation is performed according to a one-day protocol, as claimed in the present application.

The method of the present invention enables hematolymphoid cells of the recipient to be completely replaced by donor-derived cells, i.e., fully alogenic chimerism can be achieved, which is fundamentally different from the mixed allogenic chimerism taught in Ildstad (see Jin et al, *Transplantation*, 71(12):1725-1731 (2002), a copy of which is attached hereto) - the Examiner is requested to particularly note sections "Chimerism and Tolerance" (page 1727), "Evidence for Acceptance of Allogenic Skin, Pancreas, and Adrenal Glands" (page 1728), and "Discussion" (pages 1728-1730).

In this respect, the technique employed in the present invention is totally different from that taught by Ildstad, and is extremely effective in organ transplantation.

As described above, Ildstat does not disclose a technique usable for a one-day protocol by which an engraftment rate of 100% can be achieved, and therefore even applying the PV injection taught by Zhang et al in the teachings of Ildstat, it is impossible to arrive at the present invention, i.e., it would still remain a technique of organ transplantation preformed 1-7 months after the PV injection).

Furthermore, as explained on page 5 of the Amendment filed May 1, 2001, Zhang et al merely teaches a technique without irradiation (TBI). A technique that does not perform TBI is fundamentally different from those taught in Ildstad and the present invention in which irradiation (TBI) is conducted. Thus, the Examiner's combination rejection can only be made in hindsight, which is legally improper.

Moreover, it is apparent to ones skilled in the art that the results obtained by the non-TBI system (TBI dose of 0 Gy) disclosed in Zhang et al can not be applied to the TBI system of Ildstad. In other words, a skilled artisan would not foresee the effects achieved by TBI plus PV from the teachings of Ildstad in view of Zhang et al. This is clear from the Examiner's assertion that Hayashi et al and Takao et al (of record) can not be used to infer the results of Ildstad. That is, it is the Examiner's position that even in systems with irridation, if the radiation doses are different, the results can not be inferred. Thus, in view of the Examiner's assertion, there is no way that a person skilled in the art could predict that similar effects can be attained when the techniques used in a non-irradiation system are employed in a system with irridation.

In summary, the present claims have been amended to set forth an engraftment rate and a one-day administration protocol which are not taught or suggested in Zhang et al and Ildstadt. Thus, even if Ildstadt and Zhang et al were combined, the present invention would not be achieved.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Ildstad alone or when combined with the teachings of Zhang et al, and thus request withdrawal of the Examiner's rejection.

In view of the amendment to the claims, and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at the telephone number listed below on any questions that might arise.

Respectfully submitted,

Gordon Kit
Registration No. 30,764

SUGHRUE MION, PLLC
2100 Pennsylvania Avenue, N.W.
Washington, D.C. 20037-3213
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

Date: November 26, 2002

APPENDIX

Marked-Up Version of Changes

IN THE CLAIMS:

Claim 12 is being cancelled.

Claim 9 is being amended as follows:

Claim 9. (Twice Amended) A method of inducing immunological tolerance in an organ transplantation recipient which comprises the steps of:

(a) prior to organ transplantation, subjecting the recipient to total body irradiation using a sublethal radiation dose of at least 6.5 Gy, and thereafter,

(b) administering to the recipient a tolerogen effective amount of whole bone marrow cells from a graft donor by hepatic portal venous administration, and thereafter,

(c) transplanting an organ into said recipient, to thereby achieve an engraftment rate of 100%, wherein said transplanting occurs within the same day as said whole bone marrow cells are administered.